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EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,082	CRAIK ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15 and 17-26* is/are pending in the application.

4a) Of the above claim(s) *26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-13,15 and 17-25* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *06-04* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed June 23, 2004 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 1-13, 15 and 17-26 are pending.

Applicants' amendment filed June 23, 2004 is acknowledged. Applicants' response has been fully considered. Claims 1-13, 15, 17 and 18 have been amended, claim 14 has been cancelled, and new claims 20-26 have been added. Newly submitted claim 26 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claim 26 directed to a method of probing an ion channel receptor by contacting the ion channel receptor with the cyclic conotoxin and measuring a biological effect of the cyclic conotoxin on the ion channel receptor, which has different method steps and outcome from the process of preparing a cyclic conotoxin, and the method of treating a disease in mammals by administering the cyclic conotoxin peptide.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 26 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Thus, claims 1-13, 15 and 17-25 are examined.

Objection Withdrawn

3. The previous objection of claims 1-15, 17 and 18 is withdrawn in view of applicant's amendment to the claim, and applicant's response at page 6 in the amendment filed June 23, 2004.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

4. The previous rejection of claim 14 under 35 U.S.C.112, first and second paragraphs, is withdrawn in view of applicant's cancellation of the claim in the amendment filed June 23, 2004.

Informalities

The disclosure is objected to because of the following informalities:

5. Table 1 (page 8) contains amino acid sequences which are required to have "SEQ ID NO:" in the sequence listing. Applicants must comply with the requirements of the sequence rules (37 CFR 1.81-1.825) and provide a copy of sequence listing and CRF containing all the sequences.

Claim Objections

6. Claims 9 and 10 are objected to because of the use of "SEQ ID NO." or "SEQ. ID NO.". Use of "SEQ ID NO:" is suggested. See M.P.E.P. 2422.03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-9, 11-13, 15 and 17-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a specific cyclized conotoxin peptide such as

SEQ ID NOs:5-9 having two or three disulfide bonds and having an amide cyclized backbone linked at N- and C-termini, where the amino acid sequence of the cyclized conotoxin is defined; a process of preparing the cyclized conotoxin; and a composition comprising the cyclized conotoxin, does not reasonably provide enablement for a cyclized conotoxin peptide having an amide cyclized backbone with no free N- or C-terminus and having two or three disulfide bonds, where the amino acid sequence of the cyclized conotoxin is not defined; a process of preparing the cyclic conotoxin; a composition comprising the cyclic conotoxin; a method of treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity, or a method of blocking a voltage-sensitive calcium channel or nicotinic acetylcholine receptor comprising administering the cyclized conotoxin, where the cyclized conotoxin and the disease are not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-9, 11-13, 15 and 17-25 are directed to a cyclized conotoxin peptide having an amide cyclized backbone with no free N- or C-terminus and comprising two or three disulfide bonds (claims 1-9 and 20); a process of preparing the cyclized conotoxin (claims 11-13 and 19); a composition comprising the cyclized conotoxin (claims 17 and 18); and a method of treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity (claims 15 and 21-23), a method of blocking a voltage-sensitive calcium channel or nicotinic acetylcholine receptor comprising administering the cyclic conotoxin (claims 24 and 25). The specification, however, only discloses cursory conclusions without data supporting the findings, which states that cyclization of the peptide backbone of conotoxin to produce non-

natural analogs results in new molecules which can retain the therapeutic activity of the non-cyclized peptide (page 2, lines 9-11). There are no indicia that the present application enables the full scope in view of the cyclized conotoxin peptide and a method of treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity using the cyclized conotoxin as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the cyclized conotoxin peptides containing various conotoxin peptides and linker peptides, and various diseases associated with abnormal ion channel or nicotinic acetylcholine receptor activity to be treated with cyclized conotoxin peptides, which are not adequately described or demonstrated in the specification, although specific cyclic MVIIA conotoxins (SEQ ID NO:5, 6 and 7) and MII α-conotoxins (SEQ ID NO: 8and 9) have been disclosed.

(2). The absence or presence of working examples:

The specification indicates the preparation and antagonist activities of specific cyclized conotoxin such as cyclic MVIIA conotoxins (Examples 1-3, 5) and MII α-conotoxins (Example

6); three-dimensional structures of several conotoxin peptides determined by NMR spectroscopy (Example 4); and a method of determining bioavailability and stability of the cyclized conotoxin (Example 7). However, these specific examples do not provide descriptive support for a genus of numerous cyclized conotoxin peptides and various diseases to be treated with a cyclized conotoxin peptide.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Shon *et al.*, WO 96/33206) indicates μ-conotoxin PIIIA, which is a sodium channel blocker, is useful as active agent for treating urinary or fecal incontinence; and several references provided by applicants (Perez-pinzon, 1997, Z Neur. Sci, 153, 25-31, Exhibit C; Brose et al., Clin J. Pain 1997, 13(3), 256-259, Exhibit D; Verweij et al., Neurol. Res. 1997, 19(3):334-339, abstract, Exhibit E) indicate SNX-111, a synthetic product of ω-conotoxin MVIIA, is used in clinical trial for the treatment of pain and can be used to treat traumatic brain injury or stroke; Nielsen et al. (J. Mol. Biol. 1996, 263, 297-310, Exhibit A) provides a comparison of the structures of a number of ω-conotoxins, and concludes that these conotoxins share a common framework with the only difference being subtle changes in backbone conformation in loops 2 and 4, and there is structural similarity among ω-conotoxins and other classes of conotoxins such as κ-conotoxins, μO-conotoxins and δ-conotoxins; Scanlon et al., (1997, Structure 5 (12), 1585-1597, Exhibit B) indicate comparison of the structures of κ-PVIIA with ω-GVIA and conotoxin GS reveals despite differences in the three sequences, the overall fold is remarkably similar. However, the reference (e.g., Nielsen et al., 1996) indicates the positioning of positively and negatively charged and hydrophobic amino acids is quite different among these classes of conotoxins (page 307, left column, third paragraph), the specification of

the instant application also indicates the cyclization of peptide has the potential to alter the activity of the peptide, or introduce new activities (page 2, lines 28-29), and the general knowledge and level of the skill in the art do not supplement the description regarding predicting the activity of the conotoxin when it cyclized. The claims encompass numerous cyclized conotoxins, while the structures and activities of these peptides are not sufficiently described, thus the specification needs to provide specific guidance on identities and activities of various cyclized conotoxin peptides other than cyclo-MVIIA conotoxins and cyclo-MII α-conotoxins, and the effects of various cyclized conotoxin peptides in the treatment of diseases associated with abnormal ion channel or nicotinic acetylcholine receptor activity to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass numerous cyclized conotoxin peptides having an amide cyclized backbone with no free N- or C-terminus and two or three disulfide bonds, and a method of treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity disorder comprising administering the cyclic conotoxin. However, the specification does not describe the structures and activities of various cyclized conotoxin peptides other than cyclo-MVIIA conotoxins and cyclo-MII α-conotoxins, nor demonstrates the effects of these conotoxin peptides in treating various diseases. Furthermore, the specification also indicates the cyclization of peptide has the potential to alter the activity of the peptide, or introduce new activities (page 2, lines 28-29). Thus, the invention is unpredictable regarding the activity of the cyclic conotoxin and the outcome of the treatment using an unidentified cyclized conotoxin peptide. For example, Armishaw *et al.* (American Peptide Society, pages113-114, 2001) teaches the synthesis of two N

to C terminal cyclic analogs of α-conotoxin ImI (GCCSDPRCAWRC-NH_2), cImI-AG (having Ala-Gly spacer) and cImI-A (having Ala spacer), which indicates the major product of cImI-AG has 1-3, 2-4 S-S connectivity and the major isomer of cImI-A has 1-4, 2-3 S-S connectivity, while the linear α-conotoxin ImI has 1-3, 2-4 S-S connectivity (see whole document). The reference also indicates the cyclization of α-conotoxin ImI results in 30-fold decrease in receptor binding activity, and Trp10, which locates at loop 2 of the cyclic conotoxin, is significantly displaced and may be unable to interact with its receptor. Thus, despite having the three dimensional structure of ImI, which shows the close proximity of the termini and the position of the active site residues, and having experience in cyclizing peptide, the reference illustrate how unpredictable the disulfide bond connectivity and the receptor binding activity of the cyclized conotoxin are. Moreover, the specification also indicates that cyclized conotoxins, cyclo-MVIIA 1 (EC_{50}= 8.5 x 10^{-8} M for most active isomer) and cyclo-MVIIA 2 (EC_{50}= 5 x 10^{-10} M for most active isomer) have receptor binding activity decreased in 1930- and 11-fold, respectively, as compared to parent conotoxin MVIIA (EC_{50}= 4.4 x 10^{-11} M), and that not all disulfide isomers have the same level of activity (page 23, lines 19-26). This again indicates the unpredictability of the receptor binding activity of cyclized conotoxin.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a cyclized conotoxin peptide having two or three disulfide bonds and an amide cyclized backbone with no free N- or C-terminus, a process of preparing the cyclic conotoxin, a composition comprising the cyclic conotoxin, and a method of treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity, a

method of blocking a voltage-sensitive calcium channel or nicotinic acetylcholine receptor comprising administering the cyclic conotoxin. The specification indicates the preparation of cyclic MVIIA conotoxins (Examples 1, 2) and cyclic MII α-conotoxins (Example 6), and the cyclic MVIIA conotoxins act as the antagonists specific for N-type voltage-sensitive calcium channels (Example 3). The specification also indicates ω-conotoxins which block N-type calcium channels may be useful for the treatment of neurological disorders (page 15, line 23-page 16, line 1). While the specification indicates the cyclization of peptide has the potential to alter the activity of the peptide, or introduce new activities (page 2, lines 28-29), it has not shown the identities and activities of various cyclized conotoxin peptides other than cyclic MVIIA conotoxins and cyclic MII α-conotoxins. Furthermore, the specification has not demonstrated the use of any cyclized peptide in treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity. There are no working examples indicating the effects of the cyclized conotoxin peptides in treating various diseases. The claims encompass numerous cyclized conotoxins and the use of these cyclized conotoxins in treating various diseases, while the identities and activities of various cyclized conotoxin peptides and the treating conditions for various diseases are not sufficiently described in the specification. Furthermore, the activities and disulfide bond connectivity of cyclized conotoxin are not predictable in view of Armishaw *et al.* (2001) and the disclosure of specification (page 2, lines 28-29; page 23, lines 19-26). Thus, it is necessary to have additional guidance on structures and activities of various cyclized conotoxin peptides, and to carry out further experimentation to assess the effects of various cyclized conotoxin peptides in the treatment of various diseases associated with abnormal ion

channel or nicotinic acetylcholine receptor activity, the experimentation is undue because further research is required to identify a desired cyclized conotoxin in the treatment of diseases.

(6). Nature of the Invention

The scope of the claims encompass numerous cyclized conotoxin peptides and use of cyclized conotoxin peptides in treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity, but the specification only shows specific cyclic conotoxins and their activities, it has not disclosed a genus of variants of cyclized conotoxin peptides, nor has demonstrated the use of any cyclized conotoxin peptide in treating various diseases. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the outcome of treatment is unpredictable using the claimed variants, and the teachings are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the cyclized conotoxin in treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity.

In response, applicants indicate that there is no evidence of record suggesting that those skilled in the art would be unable to practice the claimed inventions. Although the Office Action provides a lengthy analysis of certain factors to be considered in assessing whether undue experimentation would be required, the analysis only indicates that any experimentation associated with the practice of the claimed inventions would be routine in nature and well within the level of skill in the art. For example, in the predictability of the art, the Office Action fails to provide any evidence demonstrating any unpredictability as to whether the claimed compounds will demonstrate some measurable level of activity. Although it might be difficult to predict

which among the claimed compounds will exhibit the highest activity, in the absence of any reason to believe that any of the claimed compounds will be entirely inactive, the mere fact that some of them might be more active than others fails to demonstrate any lack of enablement; In the amount of guidance presented/quantity of experimentation, applicant indicates the Office Action asserts that it is necessary to have additional guidance on amino acid sequences of the various cyclized conotoxin peptides, but there is no evidence of record demonstrating that those skilled in the art would, in fact, have considered such information to have been "necessary" to practice the claimed inventions; Regarding structural differences among conotoxin peptides, applicants indicate that the claimed conotoxin peptides all belong to structural classes that are characterized by common disulfide bond frameworks, and the specification provides instructions on how to cyclize conotoxin peptides generally, and ω- and α-conotoxin peptides specifically. As evidence of the structural similarity between the ω-conotoxins, and among different classes of 4-loop conotoxins, including ω-conotoxins, κ-conotoxins, μO-conotoxins and δ-conotoxins, applicants provide references by Nielsen et al. (1996, Exhibit A) and Scanlon et al., (1997, Exhibit B); Regarding the use of cyclized conotoxin peptides in the treatment of specific diseases, applicants indicate that conotoxin peptides are known to interfere with neurotransmission by targeting a variety of receptors and ion-channels, and it is widely believed that blocking those receptors or ion-channels is useful in the treatment of diseases, including neurological disorders. Applicants further provide three references (Perez-pinzon, 1997, Exhibit C; Brose et al. 1997, Exhibit D; and Verweij et al., 1997, Exhibit E) to indicate ω-conotoxin SNX-111 has entered clinical trials for the treatment of stroke and pain, and can be used to treat

traumatic brain injury, and indicate that as long as the guidance in the specification is followed, the cyclization of the peptides will not render them inactive (pages 6-11 of the response).

The response has been fully considered, however, the argument is not found persuasive because the claims are directed to numerous cyclized conotoxins having an amide cyclized backbone and two or three disulfide bonds. Since the structures and activities of the cyclized conotoxins are not defined, these cyclized conotoxins would include not only cyclization of α-conotoxins, ω-conotoxins, κ-conotoxins and μO-conotoxins with known structures as indicated in the references of Nielsen et al. (1996, Exhibit A) and Scanlon et al., (1997, Exhibit B), but also cyclization of other classes of conotoxins and derivatives of conotoxins with undefined sequences and unknown three dimensional structures, which requires additional guidance on the three dimensional structures of the cyclized conotoxins and undue experimentation to make the cyclized conotoxins with a proper peptide linker and to treat a neurological disease with a desired cyclized conotoxin, the experimentation is undue because further research is required to insert a proper peptide linker at the proper position of the conotoxin to obtain a cyclized conotoxin with a desired activity to treat a neurological disease. In the comparison of Armishaw et al. (2001) with the instant application, applicants respond with the following statement:

> The present application clearly describes the importance of considering the structural characteristics of the conotoxin peptide that is to undergo cyclization when designing the linker sequence. Once it is known that the spacing of the linker peptide can affect the connectivity of the peptide and the structure, a skilled practitioner would know to select a linker that has a sufficient number of residues for that particular conotoxin peptide. Such a selection is routine and easily performed by one of skill in the art.

This again indicates the necessity of determining the structures of the conotoxin and use of a proper peptide linker to make the desired cyclized conotoxin, the insertion of the peptide linker at the proper position of the conotoxin to make a cyclized conotoxin having a desired activity for

treatment of a neurological disease is not routine experiment because further research is needed for the selection of the desired compound and treating diseases because the treating conditions for various diseases using the cyclized conotoxin have not been disclosed. Regarding the unpredictability of the art, applicants also argue the patent law do not require any threshold level of activity, and in the absence of any reason to believe any of the claimed compounds would be inactive, the mere fact that some of them might be more active than others does not demonstrate lack of enablement. As indicated in the section of unpredictability of the art, the lack of enablement is directed to variants of cylized conotxins with undefined structures and activities. The activities of the cyclized conotoxin are required for the claimed methods of treating various diseases, which use cyclized conotoxins with activities for the treatment. MPEP 2107.02 and *In re Schert*, 566 F2d 1154 (C.C.P.A. 1977) mentioned in the response (page 8) deals with asserted utility, which is not the issue for this application. Armishaw et al. has shown the disulfide bond connectivity and the receptor binding activity of the cyclized conotoxin cannot be predicted from the parent conotoxin; and the specification only teaches specific cyclized conotoxins (e.g., cyclo-MVIIA conotoxins and cyclo-MII α-conotoxins), but the cyclization of conotoxin peptide has decreased receptor binding activity ranging from 1930 fold to 11 fold decrease. Therefore, the activities of the cyclized contotoxins with undefined structures and the effects of these compounds in the treatment of various neurological diseases cannot be predicted.

Regarding the treatment of a disease using the claimed conotoxin peptide, although conotoxin peptides are known to interfere with neurotransmission by targeting a variety of receptors and ion-channels, and a ω-conotoxin SNX-111 is used for the treatment of stroke and pain, the claimed cyclized conotoxin, which contains an extra cyclic structure, is structurally

different from the parent conotoxin peptide, and furthermore, since the activity of this cyclized conotoxin cannot be predicted from the parent conotoxin, and the specification has not described the treating conditions such as the dosage for various neurological diseases, it is necessary to carry out undue experimentation to assess the effect of the cyclized conotoxin in the treatment, the experimentation is undue because it requires further research to determine the treating conditions such as the dosage and the effect of the cyclized conotoxins. As indicated in the section above, the claims encompassed numerous cyclized conotoxins and use of the cyclized conotoxins in treating various neurological diseases, while the specification does not provide sufficient teachings regarding the claimed variants, thus the full scope of the claims is not enabled.

8. Claims 1-9, 13, 15 and 17-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-9, 13, 15 and 17-25 are directed to a cyclized conotoxin peptide having an amide cyclized backbone with no free N- or C-terminus and comprising two or three disulfide bonds; a process of preparing the cyclized conotoxin; a composition comprising the cyclized conotoxin; and a method of treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity, a method of blocking a voltage-sensitive calcium channel or nicotinic acetylcholine receptor comprising administering the cyclic conotoxin. While the specification indicates the present invention provides cyclization of the peptide backbone of

conotoxin to produce non-natural analogs which results in new molecules which can retain the therapeutic activity of the non-cyclized peptide (page 2, lines 9-11), the specification does not disclose a genus of variants for cyclized conotoxin peptides having an amide cyclized backbone with no free N- or C-terminus and comprising two or three disulfide bonds, and the use of cyclized conotoxin peptides in treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity, and in blocking a voltage-sensitive calcium channel or nicotinic acetylcholine receptor.

The specification indicates that the preparation of cyclic MVIIA conotoxins (Examples 1, 2) and cyclic MII α-conotoxins (Example 6), and the cyclic MVIIA conotoxins act as the antagonists specific for N-type voltage-sensitive calcium channels (Example 3); and omega-conotoxins which block N-type calcium channels may be useful for the treatment of neurological disorders (page 15, line 23-page 16, line 1). However, the specification does not describe a genus of variants for cyclized conotoxin peptides having an amide cyclized backbone with no free N- or C-terminus and two or three disulfide bonds; and the use of cyclized conotoxin peptides in treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity, and in blocking a voltage-sensitive calcium channel or nicotinic acetylcholine receptor. A species of the cyclized conotoxin peptide (e.g., SEQ ID NOs: 5-9) do not provide original descriptive support for a genus of cyclized conotoxin peptides and of various diseases to be treated with a cyclized conotoxin peptide. The variant compounds of the cyclized conotoxin peptide and various diseases to be treated with a cyclized conotoxin peptide do not meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled

in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Applicants have described specific examples of the cyclized conotoxin peptides (e.g., SEQ ID NOs: 5-9), however, a genus of variants for cyclized conotoxin peptides having an amide cyclized backbone with no free N- or C-terminus and two or three disulfide bonds, and various diseases to be treated with the cyclized conotoxin peptide have not been described nor disclosed.

The skilled artisan cannot envision all the contemplated compounds and all the diseases to be treated based upon the general suggestion of a functional characteristic of the cyclized conotoxin peptide. The detailed structure of the cyclized conotoxin peptide and the treating conditions for various diseases must be taught, therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of preparation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF'S were found unpatentable due to lack of written description for the broad class.

The claims are drawn to a cyclized conotoxin peptide having an amide cyclized backbone with no free N- or C-terminus and comprising two or three disulfide bonds; a process of

preparing the cyclized conotoxin; and a method of treating a disease associated with abnormal ion channel or nicotinic acetylcholine receptor activity, a method of blocking a voltage-sensitive calcium channel or nicotinic acetylcholine receptor comprising administering the cyclic conotoxin, however, the specification does not provide original descriptive support over the instantly claimed genus of variants for cyclized conotoxin peptide having an amide cyclized backbone with no free N- or C-terminus and two or three disulfide bonds, and for diseases associated with abnormal ion channel or nicotinic acetylcholine receptor activity to be treated with the cyclized conotoxin peptide.

Therefore, only those embodiments described and disclosed meet the written description requirement and not the full breadth of the claim meets the written description provision of 35 USC 1 12, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2, 6-9, 13, 15, 17-19 and 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 2 is indefinite because of the use of the term "activity". The term cited renders the claim indefinite, it is not clear what activity of the cyclized conotoxin is associated with the therapeutic treatment of mammals since the activity of the cyclized conotoxin depends on the structure of the cyclized conotoxin, which is not specified in the claim.

11. Claims 6-9 are indefinite because of the use of the term "The cyclic peptide according to claim 1 comprising a linear conotoxin peptide". The term cited renders the claim indefinite, it is not clear how the cyclic peptide can comprise a linear conotoxin peptide since the conotoxin peptide having two or three disulfide bonds is a also cyclic peptide. Claims 7-9 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

12. Claims 13 and 19 are indefinite because of the use of the term "reacting a conotoxin peptide with a linker moiety to form an extended linear conotoxin peptide". The term cited renders the claim indefinite, it is not clear how a conotoxin peptide which has disulfide bonds can react with a linker to form an extended linear conotoxin peptide; it is also not clear whether the oxidation step is needed for the formation of disulfide bond. Claim 19 is included in the rejection because it is dependent on a rejected claim and does not correct the deficiency of the claim from which it depends.

13. Claims 15 and 21-23 are indefinite because of the use of the term "a condition or disease associated with abnormal ion channel or nicotinic acetyl receptor activity". The term cited renders the claim indefinite, it is not clear which ion channel refers to, and what condition or disease is associated with abnormal ion channel or nicotinic acetyl receptor activity since the specification does not specifically identify the diseases resulting from abnormal ion channel or

nicotinic acetylcholine receptor activity. Claims 21-23 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

14. Claims 15 and 21-25 are indefinite because the claim lacks an essential step as claimed in the process of treating a disease or blocking a voltage-sensitive calcium channel or nicotinic acetylcholine receptor. The omitted step is the outcome of the treatment, it is not clear what effect the administration of an effective amount of the cyclic conotoxin would produce. Claims 21-23 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

15. Claims 17 and 18 are indefinite as to a pharmaceutically effective amount of the cyclic peptide, it is not clear what effective amount of the cyclic peptide would do?

Conclusion

16. Claims 1-9, 13, 15 and 17-25 are rejected and claim 10 is objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Patent Examiner

CMK
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